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Molecular handles on adaptive mutation

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Summary

In one experimental system, several handles on the molecular mechanism of apparent adaptive mutation have emerged. The system is reversion of a *lac* frameshift mutation in *Escherichia coli*. The molecular handles include a requirement for homologous recombination; the implication of DNA double-strand breaks as a molecular intermediate; a unique sequence spectrum of −1 deletions in mononucleotide repeats which implies polymerase errors, and also implies a failure of post-synthesis mismatch repair on those errors; and the involvement of sexual functions at some stage of the process. These molecular handles are revealing an unexpected new mechanism of mutagenesis.

Introduction

Luria and Delbrück (1943) described mutations in growing populations of bacteria. These mutations, and those described by Lederberg and Lederberg (1952), arose before they were exposed to a selection for the mutations. In contrast, adaptive mutations (Cairns *et al.*, 1988; Cairns and Foster, 1991; Foster, 1994; reviewed by Foster, 1993) or stressful-lifestyle-associated mutations (SLAM; Rosenberg, 1994) are detectable in non-growing cell populations, upon exposure to a non-lethal genetic selection, and have been found so far only in genes whose functions were selected (but see Hall, 1990). The latter may be Lamarckian. It would be important to know if this were the case.

In one experimental system, an understanding of the molecular mechanism of the adaptive mutagenesis is crystallizing. From the vantage point of a completely unravelled molecular mechanism, one will be able to address the important evolutionary implications of the existence of these mutations. It will be easier to tell what adaptive mutations are when we know how they work. The system about which the most is known, is reversion of a *lac* frameshift mutation carried on an F′ plasmid in *Escherichia coli*. This system will be the exclusive subject of this review. (For an exhaustive review of many systems refer to Foster (1993), and see Maenhaut-Michel and Shapiro (1994) for new molecular information on mutations occurring under selection in a different system whose mechanism of mutation is different, at least in part, from that described here.) Recent advances in understanding the molecular mechanism of adaptive reversion in the *lac* frameshift system are discussed in detail elsewhere (Rosenberg, 1994; Rosenberg *et al.*, 1995). These will be summarized here, the new pieces of information added, and a possible fit for all the pieces of information will be considered.

The assay system

The assay system is a +1 frameshift mutation in *lacI*, which is fused to *lacZ* such that the frameshift is polar on *lacZ* and confers a Lac⁻ phenotype. This frameshift mutation is carried on an F′ episome in cells deleted for the chromosomal *lac* operon. When plated on minimal lactose medium, growth-dependent, Luria–Delbrück mutants appear initially, on the second day after plating. Over the following week of plate incubation, adaptive revertants also appear, increasing in number linearly each day (Cairns and Foster, 1991).

Recombination

Formation of the late Lac⁺ revertants requires genes encoding the RecA (Cairns and Foster, 1991) and RecBC proteins of the RecBCD pathway of homologous recombination, whereas formation of the early revertants does not (Harris *et al.*, 1994). In recombination, RecBC enzyme prepares single-strand DNA which is then coated by RecA protein in preparation for invasion of a homologous duplex DNA molecule (see Rosenberg and Hastings, 1991). Thus, both proteins work to catalyse formation of heteroduplex recombination intermediates such as Holliday junctions.

The RecA and RecBC proteins also function in the induction of the SOS system of DNA damage repair. It is argued elsewhere that recombination, and not SOS induction, is the relevant function of these proteins in adaptive mutation (Rosenberg, 1994), and this argument is further

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